WHAT IS CLAIMED:

1. A homogeneous method of detecting cleavage of β-amyloid precursor protein (βAPP) by gamma-secretase, said method comprising detecting binding of a gamma-cleaved βAPP fragment with a pair of fluorescent adducts, wherein a first fluorescent adduct binds specifically to the carboxy-terminal end of the gamma-cleaved βAPP fragment with substantially no cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments, and wherein a second fluorescent adduct binds to the gamma-cleaved βAPP fragment within an amino acid sequence which corresponds to amino acid sequence 1-31 of β-amyloid peptide (Aβ); and wherein excitation of one of the fluorescent adducts provides a detectable transfer of energy to the other fluorescent adduct.

2. The method according to claim 1, wherein the method is practiced in a fluid sample in the presence of uncleaved βAPP and other types of gamma-cleaved βAPP fragments.

3. The method according to claim 2, wherein the sample comprises membrane fractions having endogenous gamma-secretase and Swedish variant βAPP.

4. The method according to claim 2, wherein the sample comprises solubilized gamma-secretase complex and βAPP.

5. The method according to claim 1, wherein each of the fluorescent adducts separately modifies an antibody.

6. The method according to claim 5, wherein the gamma-cleaved βAPP fragment is Aβ-40.

7. The method according to claim 6, wherein the first fluorescent adduct modifies a first antibody which binds to Aβ-40 at an epitope comprising amino acid residue 40.

8. The method according to claim 7, wherein the second fluorescent adduct modifies a second antibody which binds to Aβ at an epitope comprising amino acid sequence 1-12.

9. The method according to claim 1, wherein excitation of the first fluorescent adduct provides a detectable transfer of energy to the second fluorescent adduct.

10. The method according to claim 9, wherein the first adduct comprises a molecule selected from the group consisting of lanthanide cryptate or chelate, fluorescein, EDANS, salts of *N*-[6-amino-9-[2-carboxy-phenyl]-4,5-disulfoxy-3*H*-xanthen-3-ylidene]aminium ion (2-) and salts of 1-(epsilon-carboxypentyl-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5, 5'-disulfonate ion.

11. The method according to claim 10, wherein the first fluorescent adduct comprises a europium cryptate.

12. The method according to claim 10, wherein the second fluorescent adduct comprises xl-APC.

13. The method according to claim 12, wherein the detectable transfer of energy comprises an amplified signal from the second fluorescent adduct.

14. The method according to claim 1, wherein the other fluorescent adduct comprises a fluorescent quencher molecule.

15. The method according to claim 14, wherein the fluorescent quencher molecule is selected from the group consisting of dabcyl and salts of 9-[2-[[4-carboxy-piperidin-1-yl]sulfonyl]phenyl]-6-(*N*-methyl-*N*-phenyl-amino)-3*H*-xanthen-3-ylidene]-*N*-methylbenzenaminium ion.

16. The method according to claim 15, wherein each of the fluorescent adducts separately modifies an antibody.

17. The method according to claim 16, wherein the detectable transfer of energy comprises a decrease in fluorescent signal from the fluorescent adduct which is excited.

18. The method according to claims 13 or 17, wherein excitation is by laser, xenon flash lamp or deuterium-tungsten lamp.

19. The method according to claim 18, wherein excitation is by laser.

20. A homogeneous method for determining the presence of β-amyloid peptide (Aβ), said method comprising

(1) exposing the sample to a pair of fluorescent adducts, wherein the first fluorescent adduct binds to the carboxy-terminal region of Aβ and the second fluorescent adduct binds to the amino-terminal region of Aβ and at least one fluorescent adduct is substantially free of cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments; and

(2) detecting binding of the pair of fluorescent adducts with Aβ by excitation of one of the fluorescent adducts.

21. The method according to claim 20, wherein the first fluorescent adduct binds specifically to the carboxy-terminal end of Aβ with substantially no cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments.

22. The method according to claim 21, wherein Aβ is Aβ-40.

23. The method according to claim 22, wherein each of the fluorescent adducts separately binds specifically to either the amino- and carboxy- terminal ends of Aβ with substantially no cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments.

24. The method according to claim 21, wherein excitation is by laser, xenon flash lamp or deuterium-tungsten lamp.

25. The method according to claim 24, wherein excitation is by laser.

26. A homogeneous method for determining the presence of β-amyloid peptide Aβ-40, said method comprising

(1) exposing the sample to a pair of fluorescent adducts, wherein the first fluorescent adduct binds to the carboxy-terminal end of Aβ-40 and the second fluorescent adduct binds to the amino-terminal region of Aβ-40 and the first fluorescent adduct is substantially free of cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments; and

(2) detecting binding of the pair of fluorescent adducts with Aβ-40 by excitation of the first fluorescent adduct.

27. The method according to claim 26, wherein the first fluorescent adduct modifies a first antibody which binds to Aβ-40 at an epitope comprising amino acid residue 40.

28. The method according to claim 27, wherein the first fluorescent adduct modifies a europium cryptate.

29. The method according to claim 28, wherein the second fluorescent adduct modifies a second antibody which binds to Aβ-40 at an epitope comprising amino acid sequence 1-12.

30. The method according to claim 29, wherein the second fluorescent adduct comprises xl-APC.

31. The method according to claim 30, wherein the first fluorescent adduct is excited by laser.

32. A homogeneous method of detecting cleavage of β-amyloid precursor protein (βAPP) by gamma-secretase, said method comprising detecting binding of a 6 kDa fragment with a pair of fluorescent adducts; wherein a first fluorescent adduct binds to the amino-terminal end of the 6 kDa fragment with substantially no cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments; and wherein a second fluorescent adduct binds to a portion within the carboxy-terminal region of the 6 kDa fragment; and wherein excitation of one of the fluorescent adducts provides a detectable transfer of energy to the other fluorescent adduct.

33. The method according to claim 32, wherein each of the fluorescent adducts separately modifies an antibody.

34. The method according to claim 33, wherein one of the fluorescent adducts comprises a molecule selected from the group consisting of lanthanide cryptate or chelate, fluorescein, EDANS, salts of *N*-[6-amino-9-[2-carboxy-phenyl]-4,5-disulfoxy-3*H*-xanthen-3-ylidene]aminium ion (2-) and salts of 1-(epsilon-carboxypentyl-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5, 5'-disulfonate ion.

35. The method according to claim 34, wherein the other fluorescent adduct comprises a molecule selected from the group consisting of cross-linked allophycocyanins ("xl-APC"), coumarin, rhodamine, tetramethylrhodamine and salts of 1-(epsilon-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindodicarbocyanine-5, 5'-disulfonate ion.

36. The method according to claim 34, wherein the other fluorescent adduct comprises a fluorescent quencher molecule selected from the group consisting of dabcyl and salts of 9-[2-[[4-carboxy-piperidin-1-yl]sulfonyl]phenyl]-6-(*N*-methyl-*N*-phenyl-amino)-3*H*-xanthen-3-ylidene]-*N*-methylbenzenaminium ion.

37. A homogeneous method of detecting cleavage of β-amyloid precursor protein (βAPP) by gamma-secretase, comprising the steps of
(1) binding a first fluorescent adduct to a 6 kDa fragment and a second fluorescent adduct to either a β-amyloid peptide (Aβ) or a p3 fragment, wherein at least one of the fluorescent adducts has substantially no

cross-reactivity to other portions of uncleaved βAPP, and wherein each fluorescent adduct separately comprises either a donor molecule or an acceptor molecule; and,
(2) exciting the donor molecule by laser, xenon flash lamp or deuterium-tungsten lamp; and
(3) detecting a substantially decreased transfer of energy to the acceptor molecule.

38. The homogeneous method according to claim 37, wherein the donor molecule is selected from the group consisting of lanthanide cryptate or chelate, fluorescein, EDANS, salts of *N*-[6-amino-9-[2-carboxy-phenyl]-4,5-disulfoxy-3*H*-xanthen-3-ylidene]aminium ion (2-) and salts of 1-(epsilon-carboxypentyl-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5, 5'-disulfonate ion.

39. The method according to claim 38, wherein the acceptor molecule is selected from the group consisting of cross-linked allophycocyanins ("xl-APC"), coumarin, rhodamine, tetramethylrhodamine and salts of 1-(epsilon-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindodicarbocyanine-5, 5'-disulfonate ion.

40. The method according to claim 39, wherein the step of detecting a substantially decreased transfer of energy comprises detecting little or no amplified signal from the acceptor molecule.

41. The method according to claim 38, wherein the acceptor molecule is a fluorescent quencher molecule selected from the group consisting of dabcyl and salts of 9-[2-[[4-carboxy-piperidin-1-yl]sulfonyl]phenyl]-6-(*N*-methyl-*N*-phenyl-amino)-3*H*-xanthen-3-ylidene]-*N*-methylbenzenaminium ion.

42. The method according to claim 41, wherein the step of detecting a substantially decreased transfer of energy comprises detecting an unchanged fluorescent signal from the donor molecule.

43. A homogeneous method of screening for inhibitors of gamma-secretase cleavage in β-amyloid precursor protein (βAPP), said method comprising the steps of
(1) adding a test compound to a sample comprising gamma-secretase and βAPP;
(2) then adding a pair of fluorescent adducts to the sample, wherein a first fluorescent adduct has binding specificity to the carboxy-terminal end of a gamma-cleaved βAPP fragment with substantially no cross-reactivity to uncleaved βAPP or to other types of gamma-cleaved βAPP fragments, and a second fluorescent adduct has binding specificity to the gamma-cleaved βAPP within an amino acid sequence corresponding to 1-31 of β-amyloid peptide (Aβ), and wherein each fluorescent adduct separately comprises either a donor molecule or an acceptor molecule; and
(3) detecting a substantially decreased transfer of fluorescent energy between the fluorescent adducts after excitation of the donor molecule.

44. The method according to claim 43, wherein the donor molecule is selected from the group consisting of lanthanide cryptate or chelate, fluorescein, EDANS, salts of *N*-[6-amino-9-[2-carboxy-phenyl]-4,5-disulfoxy-3*H*-xanthen-3-ylidene]aminium ion (2-) and salts of 1-(epsilon-carboxypentyl-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5, 5'-disulfonate ion.

45. The method according to claim 44, wherein the acceptor molecule is selected from the group consisting

of cross-linked allophycocyanins ("xl-APC"), coumarin, rhodamine, tetramethylrhodamine and salts of 1-(epsilon-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindodicarbocyanine-5, 5'-disulfonate ion.

46. The method according to claim 45, wherein the step of detecting a substantially decreased transfer of energy comprises detecting little or no amplified signal from the acceptor molecule.

47. The method according to claim 44, wherein the acceptor molecule is a fluorescent quencher molecule selected from the group consisting of dabcyl and salts of 9-[2-[[4-carboxy-piperidin-1-yl]sulfonyl]phenyl]-6-(*N*-methyl-*N*-phenyl-amino)-3*H*-xanthen-3-ylidene]-*N*-methylbenzenaminium ion.

48. The method according to claim 47, wherein the step of detecting a substantially decreased transfer of energy comprises detecting an unchanged fluorescent signal from the donor molecule.

49. A homogeneous method of screening for inhibitors of gamma-secretase cleavage in β-amyloid precursor protein (βAPP), said method comprising the steps of
(1) adding a test compound to a sample comprising gamma-secretase and βAPP;
2) then binding a pair of fluorescent adducts to uncleaved βAPP; wherein a first fluorescent adduct binds to a portion within amino acid sequence 722-770 of uncleaved βAPP, a second fluorescent adduct binds to a portion within amino acid sequence 671-702 of uncleaved βAPP, and at least one of the fluorescent adducts has substantially no cross-reactivity to other portions of uncleaved βAPP, and wherein each fluorescent adduct

separately comprises either a donor molecule or an acceptor molecule; and,
(3) detecting a transfer of energy between the fluorescent adducts after excitation of the donor molecule.

50. The method according to claim 49, wherein the donor molecule is selected from the group consisting of lanthanide cryptate or chelate, fluorescein, EDANS, salts of *N*-[6-amino-9-[2-carboxy-phenyl]-4,5-disulfoxy-3*H*-xanthen-3-ylidene]aminium ion (2-) and salts of 1-(epsilon-carboxypentyl-1'-ethyl-3,3,3',3'-tetramethylindocarbocyanine-5, 5'-disulfonate ion.

51. The method according to claim 50, wherein the acceptor molecule is selected from the group consisting of cross-linked allophycocyanins ("xl-APC"), coumarin, rhodamine, tetramethylrhodamine and salts of 1-(epsilon-carboxypentyl)-1'-ethyl-3,3,3',3'-tetramethylindodicarbocyanine-5, 5'-disulfonate ion.

52. The method according to claim 51, wherein the step of detecting a transfer of energy comprises detecting an amplified signal from the acceptor molecule.

53. The method according to claim 52, wherein the acceptor molecule is a fluorescent quencher molecule selected from the group consisting of dabcyl and salts of 9-[2-[[4-carboxy-piperidin-1-yl]sulfonyl]phenyl]-6-(*N*-methyl-*N*-phenyl-amino)-3*H*-xanthen-3-ylidene]-*N*-methylbenzenaminium ion.

54. The method according to claim 53, wherein the step of detecting a transfer of energy comprises detecting a decrease of fluorescent signal from the donor molecule.

55. An isolated protein having gamma-secretase activity.

56. An isolated protein comprising gamma-secretase.

57. The isolated protein of claim 56, wherein the gamma-secretase recognizes and cleaves a substrate having a gamma secretase cleavage site.

58. The isolated protein of claim 57, wherein cleavage of the substrate by the gamma secretase at the gamma-secretase cleavage site generates a β-amyloid peptide (Aβ) and a 6kDa fragment.

59. The isolated protein of claim 56 which is a protein complex comprising gamma secretase and PS1.

60. A membrane fragment comprising gamma-secretase.

61. A method for isolating gamma-secretase from a sample by isolating gamma secretase complexed with PS1.

62. The method of claim 61, wherein isolating gamma-secretase complexed with PS1 comprises contacting the sample with an agent that recognizes and binds PS1 so that an agent/PS1/gamma secretase complex forms thereby isolating the molecule having gamma-secretase activity.

63. A molecule having gamma-secretase activity isolated by the method of claim 61.

64. The method of claim 62, wherein the agent that recognizes and binds PS1 comprises an anti-PS1 antibody.

65. A method for isolating a protein complex having gamma-secretase activity from a sample, comprising:

a) contacting the sample with a molecule that recognizes and binds PS1 so that a molecule/PS1 complex forms; and

b) removing the molecule/PS1 complex from the sample, thereby isolating the protein complex having gamma secretase activity.

66. A protein complex having gamma-secretase activity isolated by the method of claim 65.

67. The method of claim 65, wherein the molecule that recognizes and binds PS1 comprises an anti-PS1 antibody.

68. The method of claim 65, wherein the protein complex comprises gamma secretase and PS1.

69. A protein complex isolated by the method of claim 65.

70. A method for isolating a protein complex comprising gamma secretase and PS1, comprising:

a. solubilizing a gamma-secretase positive cell thereby resulting in a mixture of a protein complex comprising gamma-secretase and PS1 and other cell components; and

b. contacting the mixture with a molecule that recognizes and binds PS1 so that a molecule/PS1 complex forms; and

c. removing the complex from the other cell components thereby isolating a protein complex comprising gamma secretase and PS1.

71. A protein complex comprising gamma secretase and PS1 isolated by the method of claim 70.

72. The method of claim 70, wherein the molecule that recognizes and binds PS1 is an anti-PS1 antibody.

73. The method of claim 70, wherein in step (a) the gamma-secretase positive cell is solubilized in a solution comprising N-[3[(dimethylamino)propyl]3,7,12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

74. An isolated functionally-active substrate which is cleaved by gamma-secretase.

75. The functionally-active substrate of claim 74 comprising βAPP.

76. A method for cleaving a functionally-active substrate comprising incubating the functionally-active substrate with a molecule having gamma-secretase activity under conditions so that the molecule having gamma-secretase activity cleaves the functionally-active substrate thereby producing cleavage products.

77. A method for detecting gamma-secretase activity in a molecule of interest by determining whether the molecule can cleave a substrate in accordance with the method of claim 76.

78. The method of claim 76, wherein the functionally-active substrate comprising βAPP.

79. The method of claim 76, wherein the functionally-active substrate and the molecule having gamma-secretase activity are incubated in a solution comprising

N-[3[(dimethylamino)propyl]3,7,12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

80. A method for isolating a functionally-active substrate, comprising:

a) generating a substrate comprising a gamma-secretase cleavage sequence;

b) inserting the substrate into a microsomal membrane fragment to generate a functionally-active substrate; and

c) isolating the microsomal membrane fragment which includes the functionally-active substrate.

81. A functionally-active substrate generated by the method of claim 80.

82. The method of claim 80, wherein the substrate comprises βAPP.

83. The method of claim 80, wherein the substrate comprises the amino acid sequence as described in SEQ ID NO.: 2 or 4.

84. The method of claim 80, wherein the functionally-active substrate includes a detectable label.

85. The method of claim 80, wherein the functionally-active substrate is solubilized from the microsomal membrane fragment with a solution comprising N-[3[(dimethylamino)propyl]3,7,12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide].

86. The method of claim 80 further comprising:

a) solubilizing the functionally-active substrate from the microsomal membrane fragment; and

b) isolating the functionally-active substrate.

87. A method for identifying an agent of interest that inhibits gamma-secretase activity in a sample comprising:

a) contacting the sample and the agent of interest with a functionally-active substrate; and

b) detecting whether a cleavage product of the functionally-active substrate is generated in the sample, the lack of the cleavage product in the sample being indicative that the agent inhibits gamma-secretase activity in the sample.

88. The method of claim 87, wherein the cleavage product is detected with an antibody that recognizes and binds to the N-terminal end of the cleavage product.

89. The method of claim 87, wherein the cleavage product is detected with an antibody that recognizes and binds to the C-terminal end of the cleavage product.

90. The method of claim 87, wherein the cleavage product is detected with a pair of fluorescent adducts wherein a first fluorescent adduct binds to the N-terminal end of the cleavage product and a second fluorescent adduct binds to the C-terminal end of the cleavage product, and wherein excitation of one of the fluorescent adducts provides a detectable transfer of energy to the other fluorescent adduct.

91. The method according to claim 87 which comprises contacting a plurality of substantially identical samples each separately with a different agent of interest.

92. The method of claim 87, wherein the plurality of samples comprises more than about 10^4 samples.

93. The method of claim 87, wherein the plurality of samples comprises more than about 10^5 samples.

94. The method of claim 87, wherein the plurality of samples comprises more than about 10^6 samples.

95. The method of claim 87, wherein the plurality of substantially identical samples are each contacted essentially simultaneously with a different agent of interest.

96. A method for isolating an integral membrane protein or protein complex comprising:

a) solubilizing a cell with a solution comprising N-[3[(dimethylamino)propyl]3,7,12-trihydroxy(3a, 5b, 7a, 12a)cholan-2-amide] thereby obtaining a mixture having he integral membrane protein or protein complex and other cell components; and

b) isolating the integral membrane protein or protein complex.

97. An integral membrane protein or protein complex isolated by the method of claim 96.